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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,388	10/07/2005	Richard Ross	5585-71838-01	1917

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EXAMINER	
MERTZ, PREMA MARIA	

ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,388	ROSS ET AL.	
	Examiner	Art Unit	
	Prema M. Mertz	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *4,5,10 and 13-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-9,11,12 and 16-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892).
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/7/05*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group 1 (claims 1-18, claims drawn to a polypeptide comprising a domain set forth in SEQ ID NO:12 and a site 2 modification of glycine 120 to arginine) in the reply filed on 10/12/07 is acknowledged. The traversal is on the ground(s) that since this application is a national stage entry under 35 USC 371 of PCT/GB04/01572, the Examiner must review the claims for lack of unity under PCT Rule 13.1 and 13.2. Furthermore, Applicants argue that substituting glycine 120 in growth hormone with either arginine, lysine, tryptophan, tyrosine, phenylalanine, or glutamic acid creates a growth hormone molecule with antagonistic properties and that this Markush group recites substitutions that are all at the same residue in the molecule and share a common property in that they are all antagonists. As such, Applicants request that the Examiner reconsider the restriction requirement at it pertains to the modification of growth hormone glycine 120 and examine the species of glycine 120 substituted by an amino acid selected from the group consisting of arginine, alanine, lysine, tryptophan, tyrosine, phenylalanine and glutamic acid. However, with respect to the other disparate polypeptides listed in claim 7, Applicants argument is not found persuasive because the inventions listed as Groups I-25 do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule 13.2 they lack the same or corresponding special technical feature.

The PCT rules define a special technical feature as a feature, which defines a contribution over the prior art. The first claimed invention fails to recite such a feature,

since Benting et al (1999) teach a chimeric protein in which rat growth hormone (an unglycosylated, unpolarized secreted protein) has been modified into a glycosylphosphatidylinositol-anchored protein and then analyzed its surface delivery in polarized MDCK cells (see abstract, page 313). The protein of the reference meets the limitations of the chimeric polypeptide of Group I engineered to include a domain comprising a sequence that directs the attachment of at least one glycosylphosphatidylinositol molecule.

The Examiner will examine the modification of growth hormone comprising the domain set forth in SEQ ID NO:12 wherein the growth hormone consists of the amino acid sequence set forth in 21-254 of SEQ ID NO:2 in which glycine at amino acid 140 is substituted and examine the species of glycine 140 substituted by an amino acid selected from the group consisting of arginine, alanine, lysine, tryptophan, tyrosine, phenylalanine and glutamic acid. There is no glycine at amino acid 120 in the amino acid sequence set forth in 21-254 of SEQ ID NO:2.

The requirement is still deemed proper and is therefore made FINAL.

Claims 4-5, 10, 13-15, are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

Specification

2. The entire amino acid sequences of the domains are recited on page 3 of the specification and in claims 3-5. It is suggested that the amino acid sequences in the specification be identified by the appropriate sequence identifier as set forth in the "Sequence Listing" as required by 37 CFR § 1.821(d) and in the claims, Applicants are

requested to delete the recitation of the sequences from claims 3-5 and only recite the SEQ ID NO. Furthermore, reciting the entire amino acid sequence in the claim is awkward, difficult to consider and increases the possibility of printer errors.

Claim Rejections - 35 USC § 101

3. 35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claim 1 is rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter. The claims embrace a use of the chimeric polypeptide as a pharmaceutical and there are no provisions for "a use" in the statutes. Amending the claim to delete this limitation will obviate this rejection, but does not prevent the Examiner from making the next office Action final.

In view of the improper format for claim 1, this claim will be examined for a reasonable interpretation of its intended meaning.

Claim Rejections - 35 USC § 112, first paragraph, written description

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4a. Claims 1-3, 6-9, 11-12, 16-18 are rejected under 35 U.S.C. 1 12, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a chimeric polypeptide engineered to include a domain comprising a sequence that directs the attachment of at least one glycosylphosphatidylinositol molecule, wherein said polypeptide is not a ligand binding domain of a cytokine receptor and wherein the polypeptide has been modified by addition, deletion or substitution of at least one amino acid residue to provide a sequence variant of said polypeptide.

The claims do not require that the polypeptide possess any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polypeptides that is defined only as a chimeric polypeptide comprising a sequence that directs the attachment of at least one glycosylphosphatidylinositol molecule. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved for the biological activity desired. Accordingly, in the absence of sufficient recitation of

distinguishing identifying characteristics and structure/function relationship, the specification does not provide adequate written description of the claimed genus.

Vas-cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the ad that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the written description' inquiry, whatever is *now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that (he or she) invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF'S were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. Therefore, only a nucleic acid encoding a polypeptide of amino acid sequence set forth in SEQ ID NO:466 as recited in claim 63, but not the full breadth of the claims meets the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

4b. Claims 1-3, 6-9, 11-12, 16-18, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a growth hormone polypeptide comprising a domain of amino acid sequence set forth in SEQ ID NO:12 that directs the attachment of at least one glycosylphosphatidylinositol molecule, said growth hormone consisting of the amino acid sequence set forth in 21-254 of SEQ ID NO:2 in which glycine at amino acid 140 is substituted by an amino acid selected from the group consisting of arginine, alanine, lysine, tryptophan, tyrosine, phenylalanine and glutamic acid, does not reasonably provide enablement for a chimeric polypeptide as set forth in claims 1 or 8. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claim 1, for example, is overly broad in its limitation of "a chimeric polypeptide", claim 2 recites "variant" and claim 8 recites "said polypeptide has been modified by addition, deletion or substitution of at least one amino acid residue to provide a sequence variant of said polypeptide" because no guidance is provided as to which of the myriad of polypeptides encompassed by the scope of the claims will retain the characteristics of the desired polypeptide. Variants of a nucleic acid can be generated by deletions, insertions, and substitutions of nucleotides, but no actual or prophetic examples on expected performance parameters of any of the possible variants of the claimed growth hormone polypeptide molecule or muteins of the growth hormone protein molecule have been disclosed. Furthermore, it is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. For example, Mikayama et al. (1993) teaches that the

human glycosylation-inhibiting factor (GIF) protein differs from human migration inhibitory factor (MIF) by a single amino acid residue (page 10056, Figure 1). Yet, despite the fact that these proteins are 90% identical at the amino acid level, GIF is unable to carry out the function of MIF, and MIF does not exhibit GIF bioactivity (page 10059, second column, third paragraph). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph).

There is no guidance provided in the instant specification as to how one of skill in the art would generate and use a polypeptide that has been modified by addition, deletion or substitution of at least one amino acid residue to provide a sequence variant of said polypeptide other than the growth hormone polypeptide comprising a domain of amino acid sequence set forth in SEQ ID NO:12 that directs the attachment of at least one glycosylphosphatidylinositol molecule, said growth hormone consisting of the amino acid sequence set forth in 21-254 of SEQ ID NO:2 in which glycine at amino acid 140 is substituted by an amino acid selected from the group consisting of arginine, alanine, lysine, tryptophan, tyrosine, phenylalanine and glutamic acid, exemplified in the specification. See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if

experimentation is necessary, it is undue. The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Given the breadth of the claims, in light of the predictability of the art as determined by the number of working examples, the level of skill of the artisan, and the guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

Claim Rejections - 35 USC § 112, second paragraph

5. Claims 1-3, 6-9, 11-12, 16-18, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rejected as vague and indefinite for the following reasons.

Claim 1, line 1, is vague and indefinite because the metes and bounds of the limitation "chimeric polypeptide" is undeterminable. It is suggested that the claim be amended to recite the growth hormone polypeptide intended to be claimed.

Regarding claim 1, the phrase "engineered to include" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 1, line 4, is improper because it recites "for use as a pharmaceutical". It is suggested that the claim be amended to recite a pharmaceutical composition.

Claim 2, line 2, recites "variant". The metes and bounds of this term with respect to the upper limit on the number of additions, deletions and substitutions is unclear.

Claim 3 is rejected as improper because the entire amino acid sequence of the domain is recited in the claim. It is suggested that the amino acid sequence be identified only by the appropriate sequence identifier. Applicants are requested to delete the recitation of the sequences from claim 1 and only recite the SEQ ID NO. Furthermore, reciting the entire amino acid sequence in the claim is awkward, difficult to consider and increases the possibility of printer errors.

Regarding claim 6, the phrase "includes" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 7 is improper because it recites non-elected polypeptides. It is suggested that the non-elected polypeptides be deleted from the claim to obviate this rejection.

Claim 8 is vague and indefinite because it recites the limitation "at least one amino acid residue". The upper limit on the number of additions, deletions and substitutions to obtain a "variant" of the polypeptide is unclear.

Claim 9 is vague and indefinite because it recites the limitation "at least one growth hormone receptor binding domain". The upper limit on the number of growth hormone receptor binding domains is unclear.

Claim 11, line 2, is vague and indefinite because it recites "site 2". The metes and bounds of this term are unclear.

Claim 12, line 2, is vague and indefinite because it recites "site 1 and site 2". The metes and bounds of these terms are unclear.

Claim 16 is rejected as vague and indefinite for the following reasons.

Claim 16 is vague and indefinite because it recites "glycine 120". This is incorrect because there is a serine at 120. The claim should properly recite "glycine 140".

Claim 16 is rejected as improper because it recites both the Figure number and the amino acid sequence identifier. It is suggested that the Figure number be deleted form the claim because recitation of both the Figure number and the amino acid sequence identifier is repetitious as well as confusing.

Claim 17, line 2, is vague and indefinite because it recites "site 2". The metes and bounds of this term are unclear.

Claim 18 is vague and indefinite because it recites "glycine 120". This is incorrect because there is a serine at 120. The claim should properly recite "glycine 140".

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 7-9, 11-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Benting (1999).

Benting et al (1999) teach a chimeric protein in which rat growth hormone (an unglycosylated, unpolarized secreted protein) has been modified into a glycosylphosphatidylinositol-anchored protein and then analyzed its surface delivery in polarized MDCK cells (see abstract, page 313; Figure 1, page 315). The protein of the reference meets the limitations of the chimeric polypeptide of claim 1 engineered to include a domain comprising a sequence that directs the attachment of at least one glycosylphosphatidylinositol molecule wherein the polypeptide is growth hormone modified to produce a variant of the polypeptide engineered to include a domain comprising a sequence that directs the attachment of at least one glycosylphosphatidylinositol molecule, wherein said polypeptide is not a ligand binding domain of a cytokine receptor.

Conclusion

No claim is allowed.

Claims 1-3, 6-9, 11-12, 16-18 are rejected.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Prema Mertz whose telephone number is (571) 272-0876. The examiner can normally be reached on Monday-Friday from 7:00AM to 3:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on (571) 272-0835.

Official papers filed by fax should be directed to (571) 273-8300. Faxed draft or informal communications with the examiner should be directed to (571) 273-0876.

Information regarding the status of an application may be obtained from the Patent application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Prema Mertz/
Primary Examiner
Art Unit 1646